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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,319	08/19/2003	Michael D. Ruff	M233 1030.1	3826

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EXAMINER	
SILVERMAN, ERIC E	
ART UNIT	PAPER NUMBER
1618	

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04/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/643,319	RUFF ET AL.	
	Examiner	Art Unit	
	Eric E. Silverman, PhD	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-46,49-53 and 55-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-46,49-53 and 55-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant is advised that the Examiner assigned to this Application has changed. The Examiner currently assigned to this Application is **Eric Silverman, PhD**, whose contact information can be found at the end of this action. Applicant is further advised that this Application is currently assigned to **Art Unit 1615**.

Applicants' submission filed 3/11/2008 has been received. Claims 43 – 46, 49 – 53, 55 – 66 are pending in this action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58 – 66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

The originally filed disclosure does not disclose or describe a formulation having a particulate pharmaceutical substrate that is exclusively monobasic calcium phosphate, or exclusively tribasic calcium phosphate, or exclusively anhydrous dibasic calcium phosphate, as recited in these claims. While the disclosure does describe the substrates containing each of these, the disclosure does not describe excluding other materials or excipients from the substrate. Note that the substrate of claim 43, which is

exclusively dibasic calcium phosphate dihydrate, is disclosed in an example, and thus claim 43 is *not* included in this rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 43 – 46, 49 – 53, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,958,458 to Norling et al. in view of US 5,788,987 to Busetti et al.

Norling teaches pharmaceutical formulations in the form of coated cores. The core material, which is equivalent to the substrate of instant claims, is selected from materials such as calcium carbonate, calcium silicate, calcium phosphate, etc. See Abstract. The core may have two coatings, one having an active agent, and one being for the purpose of modifying the release of the active. The active agent may be insulin. See col. 7, lines 60 —67. Palsticizers such as castor oil, mineral oil, and coconut oil, or film coating polymers may be included in the coating. See cols. 9 and 10. The other coating may be, for example, an enteric coating, which the artisan recognizes is applied over the active agent coating, and may contain film forming polymers such as EUDRAGIT. See cols. 9 and 10.

What is lacking is a teaching of the use of dibasic calcium phosphate dihydrate as the only core excipient, and tablets or capsules made from the particles..

Busetti teaches controlled release dosage forms for peptide drugs, such as insulin. Col 4, liens 33 - 38. The core may consist of materials such as dibasic calcium phosphate dihydrate. Col. 4, lines 39 - 50. Because Busetti teaches that the core may have "one or more" of the materials, it is understood that Busetti is suggestive of using the listed materials alone. Busetti also teaches that the particles may be pressed into tablets or filled into capsules. Col. 5, lines 19 - 24.

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to use the core material of Busetti in as the core (substrate) of Norling, which would give the instantly claimed invention. Obviousness stems from the fact that the claims are no more than a combination of well known components wherein each component serves its recognized, predictable purpose and gives a predictable result. Dibasic calcium phosphate dihydrate is recognized as being useful as a core (substrate) for insulin delivering compositions in Busetti. In Norling, it is recognized that insulin may be coated onto an inactive core to make a delivery device. The specific coating excipients used in the instant claims are also recognized by Norling. The art also recognizes that making tablets or capsules out of particles is useful for ease of administration, as discussed in Busetti. Accordingly, the instant claims are no more than the use of Norling's insulin coatings on inert cores recognized by Busetti to be useful for insulin delivery, wherein the result of such use is a delivery system for insulin. The evidence of record does not indicate any significant difference between the

properties of the claimed insulin delivery system and other similar systems where insulin is coated on a different inert core, as in Norling. The difference between the instant claims and Norling is no more than changing the nature of the inert core, however, Busetti recognizes that the instantly claimed inert core is useful for insulin delivery. Because the evidence does not show any difference between the use of one inert core and another inert core, but rather suggests that the result is merely that which the artisan would expect from changing the nature of the core (namely, a device similar to Norling's), the claimed composition would have been prime facie obvious at the time of the invention.

Claims 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,958,458 to Norling et al. in view of US 5,788,987 to Busetti et al as applied to claims 43 – 46, 49 – 53, and 55 above, and further in view of US 2003/0050228 to Ekwuribe et al.

What is lacking from Norling and Busetti are the specific insulin drugs of instant claims.

Ekwuribe teaches that for oral administration, insulin polypeptides such as HIM2 (the polypeptides of instant claims) are advantageous. Paragraphs 0133 – 0134. Solid formulations for oral administration are disclosed. Paragraph 0145.

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to use the insulin polypeptides of Ekwuribe as the insulin in Norling. Obviousness stems from Ekwuribe's suggestion that these polypeptides are particularly useful for oral administration.

Claims 58 – 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,958,458 to Norling et al. in view of US 5,788,987 to Busetti et al as applied to claims 43 – 46, 49 – 53, and 55 above, and further in view of US 6,358,532 to Starling.

What is lacking from Norling and Busetti is the teaching of the calcium phosphates of instant claims, such as calcium phosphate tribasic.

Starling teaches the use of beads that comprise calcium phosphate tribasic in pharmaceuticals. Claim 1, example 6. The beads may be coated with a biological (active agent) coating. Claim 2.

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to use calcium phosphate tribasic as the inert core of Norling and Busetti. Obviousness stems from the fact that the instant claims are no more than the use of old familiar components in a manner which yields predictable results. Norling teaches coat insulin on inert cores to make a drug delivery system. Starling teaches that the inert cores (substrates) of instant claims may be coated with drugs to make a drug delivery system. Busetti goes to the expectation of success, by teaching that insulin is compatible with closely related inert cores. The result of instant claims, using the cores of Starling with the coatings of Norling, is an insulin delivery system. There is no evidence of record that would indicate that the claimed delivery system has any property that is significantly different from those of the art. Because the evidence does not show any difference between the use of one inert core and another inert core, but rather suggests that the result is merely that which the artisan would expect from

changing the nature of the core (namely, a device similar to Norling's), the claimed composition would have been prime facie obvious at the time of the invention.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is further established that a prime facie holding of obviousness based on the teachings of more than one reference, cannot be rebutted by arguing against only one of the references; rather the teachings of the art as a whole must be considered. In the instant case, Applicants' arguments are directed only at the Norling reference, and completely disregard the teachings of the other references. Although Applicants aver that Norling does not render the claims obvious, the rejections of record are over Norling in view of other references, not over Norling alone. Applicants' arguments fail to address the teachings of all of the cited prior art and accordingly, the arguments cannot be persuasive.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric E. Silverman, PhD whose telephone number is (571)272-5549. The examiner can normally be reached on Monday to Thursday 7:00 am to 5:00 pm and Friday 7:00 am to noon.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571 272 0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

Eric E. Silverman, PhD
Art Unit 1618